Gabapentin for Alcohol Withdrawal: Gaba-gaba-doo, yet another use? We've got some work to do now.

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Objectives
• Discuss the importance of classifying alcohol withdrawal severity
• Identify treatment gaps of current treatment options for alcohol withdrawal
• Evaluate existing literature on gabapentin use in alcohol withdrawal disorder

Alcohol Use Disorder
• 5-10% of world’s population affected by alcohol use disorder
  – Problematic pattern of alcohol use
  – Tolerance
  – Withdrawal

Alcohol Withdrawal Syndrome (AWS)
• Cluster of symptoms occurring in individuals with alcohol dependence
  – Mild to severe
    • Tremor, tachycardia, nausea/vomiting, seizures, hallucinations, agitation, delirium tremens

Severity

Conflict of Interest
• The author of this presentation has no conflicts of interest to disclose
Severity

- Tremor
- Tachycardia

Mild
Moderate
Severe

Nausea/
Vomiting
Agitation

Seizures
Delirium Tremens (DTs)

Symptom Timeline

- Insomnia, tremors, anxiety, GI upset, headache, diaphoresis, palpitations, nausea, tachycardia, hypertension

Diagnosis

- Amount and frequency of alcohol ingestion
- History of previous hospitalizations
  - Prior seizures?
  - Prior DTs?
- Relation between cessation of alcohol intake and onset of symptoms


Symptom Timeline

- Insomnia, tremors, anxiety, GI upset, headache, diaphoresis, palpitations, nausea, tachycardia, hypertension

Diagnosis

- Amount and frequency of alcohol ingestion
- Relation between cessation of alcohol intake and onset of symptoms
- History of previous hospitalizations
- Severity assessment: Clinical Institute Withdrawal Assessment for Alcohol (CIWA)


CIWA Scale

- Anxiety
- Confusion
- Restlessness
- Mood
- Memory
- Nausea
- Heart Rate
- Sleep Quality
- Diaphoresis

Symptom Assessment

- None (0 points)
- Mild (1 point)
- Moderate (2 points)
- Severe (3 points)

Severity Assessment

- ≤ 8 points: Mild
- 9-15 points: Moderate
- ≥ 15 points: Severe

Treatment Plan

Goal:
1. Provide safe withdrawal
2. Use least amount of medicine possible to achieve rapid detoxification (CIWA)
3. Prepare patient for on-going treatment of alcohol dependence


Pathophysiology

- Nutritional deficiencies
- Interruption of constant CNS exposure to alcohol
  - Decrease in GABA levels and GABA-receptor sensitivity
  - Nervous system hyperactivity in absence of alcohol

Pharmacotherapy

- Benzodiazepines (gold standard)
  - Diazepam, lorazepam, chlordiazepoxide
- Barbiturates
  - Phenobarbital
- Anticonvulsants
  - Carbamazepine (CBZ), valproic acid (VPA), gabapentin
- Adrenergic medicines
  - Clonidine, propranolol

Clinical Dilemma with Benzodiazepines

- Increased craving
- Early relapse
- Increased alcohol consumption
- Memory deficits
- Respiratory depression
- Drug-drug interactions
- ABUSE

Pharmacotherapy Goals

- No seizures
- Reduces craving
- Relapse risk
- Low abuse potential
- Lacks DDIs
- ↓ AW symptoms

BZDs

Ideal Agent

Minimal SE’s

Pharmacotherapy

↑ Dopamine
  Hallucinations

↑ NM达
  Delirium Tremens

↑ Glutamate
  Seizures

↑ Noradrenaline
  Adrenergic Storm

↓ GABA
Pharmacotherapy Goals

BARBITURATES
- Minimal SE's
- No seizures or DTs
- Reduces craving
- Lacks DDIs
- ↓ Relapse risk
- ↓ AW symptoms

ADRENERGICS
- Minimal SE’s
- No seizures or DTs
- Reduces craving
- Lacks DDIs
- ↓ Relapse risk
- ↓ AW symptoms

ANTI-CONVULSANTS
- Minimal SE’s
- No seizures or DTs
- Reduces craving
- Lacks DDIs
- ↓ Relapse risk
- ↓ AW symptoms

Gabapentin
- GABA analogue
- Anti-convulsive and anxiolytic properties
- Good tolerability and favorable safety profile
- Pure renal elimination
- Reduces craving and relapse risk
- Inexpensive

Bonnet, et al. (1999)
- Four inpatients with moderate AWS and alcohol dependence for over five years
- Received gabapentin 400 mg QID
- Compared as-needed clomethiazole (CLO) requirements to previous admission
- Gabapentin led to reduced CLO requirements, no documented seizure occurrences

Bonnet, et al. (2003)
- Objective: To assess efficacy of gabapentin in the treatment of AWS
- Design: 2-center, double-blind, placebo-controlled
- Population: Moderate-Severe AWS according to MAWS Scale (57 total patients)
- Interventions: Gabapentin 400 mg QID vs. placebo • Patients received as needed clomethiazole (CLO)
- Outcomes: Primary: Amount of rescue CLO needed • Secondary: Course of MAWS scores within first 48 hours of AWS

MAWS = Mainz Alcohol Withdrawal Score

Bonnet, et al. (2003)

**Results**
- No difference in number of CLO taken in initial 24 hours (P=0.96)
- MAWS in first 48 hours not significantly different (P=0.39)
- No seizures or delirium throughout treatment

**Limitations**
- Gabapentin dose may have been too low
- Design quickly led to “rescue”
- Clomethiazole may mask delayed effect of gabapentin

**Conclusion**
- Gabapentin 400 mg qid no better than placebo in reducing need for rescue clomethiazole for treatment of AWS

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Mariani et al. (2006)

**Objective**
- To assess efficacy of gabapentin in the management of AWS

**Design**
- Open-label, randomized, controlled trial

**Population**
- Inpatient detoxification patients with CIWA score > 10 and DSM—IV criteria for alcohol dependence (n=27)

**Interventions**
- Gabapentin taper (2400 mg first 24 hours, daily dose reduction 600 mg)
- Phenobarbital taper (60 mg QID, daily dose reduction 60 mg)

**Outcomes**
- Primary: Proportion of treatment failures (need for ≥ 3 doses of breakthrough phenobarbital)

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Mariani et al. (2006)

**Results**
- No difference in proportion of treatment failures
- No difference in AWS symptoms (craving, mood, anxiety)

**Limitations**
- Open-label (bias), small sample size
- PRN phenobarbital could confound gabapentin effect
- Dosing schedule of gabapentin potentially suboptimal

**Conclusion**
- Gabapentin may be equivalent to phenobarbital in the treatment of alcohol withdrawal

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Myrick, et al. (2009)

**Objective**
- To evaluate alcohol use and symptom reduction of gabapentin compared to lorazepam in the treatment of AWS

**Design**
- Double-blind, randomized, dose-response trial

**Population**
- Outpatient detoxification patients with CIWA scores ≥ 10 (n=100)

**Interventions**
- Lorazepam 6 mg tapering to 4 mg over 4 days
- Gabapentin (either 900 mg tapering to 600 mg or 1200 mg to 800 mg)

**Outcomes**
- Severity of alcohol withdrawal (CIWA scores) days 1-4 and days 5, 7, 12
- Alcohol use, measured via verbal report and alcohol breath levels

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Myrick, et al. (2009)

**Results**
- CIWA score reduction superior in gabapentin group
- Lorazepam group higher probability of relapse
- Less craving, anxiety, and sedation in gabapentin group

**Limitations**
- Only moderate AWS severity
- Participants in better general health
- Small sample size

**Conclusion**
- Gabapentin was superior to lorazepam in the treatment of outpatients in moderate AWS (lower probability of drinking and clinically similar symptom reduction)

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Bonnet, et al. (2010)

**Objective**
- To test a higher gabapentin entry dose in treating AWS

**Design**
- Open-label trial

**Population**
- Patients with CIWA scores ≥ 15 (n=37)

**Interventions**
- Entry dose 800 mg gabapentin given at baseline
- Early-responders: 600 mg QID taper; Non-early responders: usual tx

**Outcomes**
- CIWA, HAMA, HAMD score trend over four-day treatment course
- Adverse clinical effects throughout treatment course
Bonnet, et al. (2010)

Results
- CIWA < 15 in 27 (73%) patients after gabapentin load
- Two "early-responders" developed seizures
- "Non-responders": more severe AWS (P<0.026), longer treatment duration (P<0.001)

Limitations
- Open-label, small sample size, lack of comparator
- Lack of generalizability

Conclusion
- Non-response to gabapentin can be predicted by more severe AWS (mean CIWA score >20) with greater anxiety/depressive symptoms

Clinical Trial Summary

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<tbody>
<tr>
<td>Population</td>
<td>Moderate AWS</td>
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<td>Severe AWS</td>
<td>CIWA &gt; 10</td>
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<tr>
<td>Intervention</td>
<td>Gabaa 400 mg</td>
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<td>CIWA + 30</td>
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<td>Population</td>
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<tr>
<td>Results</td>
<td>Reduced need for rescue medication</td>
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<td>CIWA reduction</td>
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<tr>
<td>Conclusion</td>
<td>Gabaa reduces need for rescue medication</td>
<td>Gabaa does not reduce need for rescue</td>
<td>Gabaa superior to phenobarb in AWS treatment</td>
<td>Gabaa load helpful only in reducing less severe AWS</td>
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What do YOU think?

Dose?
- 400 mg QID?
- 600 mg TID?
- Loading strategy?

Population?
- Inpatient?
- Outpatient?

Outcomes?
- PRN requirements?
- MAWS reduction?
- CIWA reduction?
- Mood?

Pharmacotherapy Goals

- Reduces AW symptoms
- BZD
  - Seizure prevention: X
  - Low side-effect incidence
  - Few drug-drug interactions
  - Low potential for abuse
  - Decreases craving
  - Decreases relapse

- Reduces AW symptoms
- GABA
  - Seizure prevention: X
  - Low side-effect incidence
  - Few drug-drug interactions: X
  - Low potential for abuse: X
  - Decreases craving: X
  - Decreases relapse: X
Why not both?

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<th>Reduces AW symptoms</th>
<th>BZD + GABA</th>
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<tr>
<td>Decreases relapse</td>
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Future Direction

- Research Proposal
  - To investigate the use of adjunctive gabapentin with BZDs in the treatment of inpatient AWS
  - Primary Objective: determine whether adjunctive gabapentin leads to reduction in PRN BZD administration
  - Secondary Objective: evaluate whether adjunctive gabapentin leads to quicker, better treatment of AWS

Conclusion

- Gabapentin effectively treats mild-moderate AWS
- Gabapentin effectively treats alcohol dependence
- Gabapentin is safe, and well-tolerated
- BZDs are current gold standard, but possess several limitations
- Mixed results regarding gabapentin ability to reduce need for rescue medication in AWS

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